

Remarks

This amendment accompanies a Request for Continued Examination (RCE) of the application. Reconsideration of the rejection is requested in view of the foregoing amendments and the accompanying remarks.

Support for Amendments

Support for the amendment of claim 1 is found at page 6, lines 23-26. Claim 2 contains the language of claim 1 that has now been moved into claim 2. Claim 4 restates the same language that was already present in that claim to avoid the use of the method language that the examiner had previously disregarded. Claim 6 is supported at page 18, lines 16-20. Claim 7 is supported at page 21, lines 3-5. Claim 8 is supported at page 24, lines 26-31.

Claim 1

Claim 1 had been rejected as obvious in view of Boehringer et al. (WO 98/39657) which was said to show all the structural limitations of the claims. In particular, the October 18, 2005 Office action stated that Boehringer et al. disclosed a test strip having a mobilization zone containing a mobilizable tracer, as well as sample application and primary and secondary capture areas with similar reagents as in claim 1 of the pending application. The Office action concludes that “since Boehringer teaches the same materials in the same order Boehringer would achieve the separation of wave fronts that allows the analyte to reach the primary capture zone first. Applicant has not recited anything different than the prior art.”

However, all embodiments of the Boehringer device are designed to perform “non-bibulous” flow which is defined at page 31, lines 17-23:

By “non-bibulous lateral flow” is meant liquid flow in which all of the dissolved or dispersed components of the liquid are carried at substantially equal rates and with relatively unimpaired flow, laterally through the membrane or matrix, as opposed to preferential retention of one or more components as would occur, e.g., in materials capable of adsorbing or imbibing one or more components.

Boehringer is replete with repeated teachings of “non-bibulous” flow. The abstract unequivocally states that the “capture zones are disposed on a nonbibulous matrix.” The device of FIG. 1 is also a “non-bibulous flow” matrix (page 15, lines 15-16), and the test is performed under “non-chromatographic conditions” (page 17, lines 29-30). Boehringer teaches at page 24, lines 27-28 that the “matrix is preferably a blocked nitrocellulose capable of non-bibulous flow.”

Boehringer notes that bibulous flow is preferred in the prior art (page 31, lines 23-24), but it is clear that the Boehringer reference teaches the importance of non-bibulous flow. Boehringer incorporates by reference a number of prior patents and patent applications, such as U.S. Patent No. 4,943,522 which explicitly teaches away from bibulous flow because it is said to reduce sensitivity (column 4, lines 25-39), and U.S. Application No. 07/639,967 which eventually issued as U.S. Patent No. 5,770,460, which teaches that bibulous flow is to be avoided because it slows the assay. The incorporated ‘460 patent teaches that the lateral flow assays can be improved by the application of blocking agents that obscure the interactive forces that account for the bibulous nature of the substrates (column 3, lines 27-30). In particular, the substrate is rendered nonbibulous by saturating it with methylated bovine serum albumin (methylated BSA) (column 7, lines 16-18). Incorporated Application No. 07/639,967 (which teaches the importance of avoiding bibulous flow) is explicitly referenced at page 38, lines 2-4 of the Boehringer reference as disclosing the methods by which the lateral flow assay device in Boehringer is prepared. See also Boehringer at page 32, lines 23-28, which teaches that non-

bibulous flow is provided by treating nitrocellulose membranes with a blocking agent such as methylated BSA.

Both U.S. Patent No. 4,943,522 and application 07/639,967 (eventually issued as U.S. Patent No. 5,770,460) were incorporated by reference in Boehringer at page 10, lines 24-29, and again at page 61, line 33 to page 62, line 2. According to MPEP 2163.07(b), the “information incorporated [by reference] is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed.” Hence the teachings against bibulous flow are part of the Boehringer specification, and must be considered as part of its teaching. It should also be noted that the incorporated U.S. Patent No. 4,943,522 and application 07/639,967 have at least one inventor (Provonost) in common with the Boehringer et al. application, and all these references share a common assignee. The teachings against bibulous flow are consistent with this context.

Although the absorbent zone of the Boehringer device is said to be capable of bibulous flow (page 33, lines 23-24), every example of the Boehringer devices is a test strip in which this capability is intentionally incapacitated because the sample receiving, labeling and capture zones are rendered non-bibulous by saturating them with methylated-BSA. See page 38, lines 13-16; page 39, lines 1-3; page 44, lines 16-20. Other examples of the test strip were described in Boehringer at page 53, lines 24-26, as having intermediate and capture zone membranes that “were prepared identically to those used for the Lateral Flow Assay Device used in the dry reagent assay formats (Figure 1).” The description of all subsequent embodiments of the device in Boehringer refer back to the methylated-BSA-impregnated test strips of the earlier embodiments, or explicitly state that the nitrocellulose strips are blocked with methylated-BSA. See, for example, Boehringer at page 56, line 25; page 58, lines 34-35; and page 60, lines 19-20.

In summary, applicants submit that the Office action incorrectly relies on Boehringer as teaching a disclosure of the same materials in the same order to achieve the same result. The incorporated references (which must be considered to be part of the Boehringer application) explicitly teach away from chromatographic flow in which separation of the tracer and analyte would occur, because such chromatographic flow is said to be inefficient, time-consuming, and lacking in sensitivity. Every example in the Boehringer reference itself follows that teaching by blocking the nitrocellulose with methylated-BSA to abolish chromatographic flow. The teachings and specific examples of Boehringer are the antithesis of the presently claimed invention in which “the bibulous substrate permits sequential migration of the analyte and analog so that the analyte migrates in advance of the detectable tracer” (amended claim 1). Blocking the chromatographic flow prevents the claimed sequential migration of the analyte and analog. Boehringer does not disclose the claimed test strip. The incorporated references in Boehringer (which share a common inventor with the Boehringer reference) make it clear that the inventors considered differential chromatographic flow through the test strip to be inefficient and undesired.

A prima facie case of obviousness has not been established, because the Boehringer reference does not disclose any test strip in which the claimed differential flow occurs, and Boehringer’s co-inventor’s prior art references, which are incorporated into the Boehringer reference, make clear that the inventors discouraged the use of chromatographic flow.

Claims 2-5 and 7

Claim 2 states that the tracer is present on the test strip in a position that the distal flow of tracer through the bibulous substrate reaches the primary capture area after the distal flow of

analyte. Boehringer does not disclose such a feature, because in all instances Boehringer teaches that the capture zone of the matrix is non-bibulous.

Claim 3 states that the tracer is heavier than the analyte and migrates through the test strip at a rate slower than the analyte. Boehringer can not be said to show such a device, because all the embodiments of Boehringer have a capture zone that is blocked to avoid such sequential flow.

Claim 4 states that the tracer interacts with the test strip to slow migration of the tracer relative to migration of the analyte. This is the opposite of the test strip in Boehringer in which the tracer interacts with the methylated-BSA-blocked test strip to assure uniform migration of the tracer and the analyte through the non-chromatographic test strip. Claim 5 similarly calls for a larger tracer to migrate more slowly than the analyte, contrary to the non-chromatographic test strip of Boehringer which has been treated with methylated-BSA to avoid separate migration of the tracer and analyte. Claim 7 states that the polarity or charge interacts with the bibulous substrate to retard migration, which achieves the opposite effect of the methylated-BSA-blocked test strip of Boehringer. The cited reference does not establish a prima facie case of obviousness with respect to these claims, because they would require modifying the methylated-BSA blocked test strips in the examples of Boehringer in a manner that would be contrary to the reason Boehringer treated the test strips with methylated-BSA.

Claim 6

Claim 6 states that the detectable tracer is positioned beneath the surface of the test strip along which the liquid sample migrates to the primary and secondary capture area such that the tracer migrates through the test strip to the primary capture area more slowly than analyte in the

liquid sample that migrates along the surface of the test strip. The Office actions of July 26 and October 18, 2005 had cited Fredrickson as teaching a tracer beneath the surface of the test strip. The Office action contended that Fredrickson taught a tracer impregnated in a mobilization zone, and that such impregnation would mean the tracer was below the surface of the test strip. However, as shown in FIG. 1 of Fredrickson, the tracer is in fact impregnated in a conjugate pad 3 that is *layered on top* of the membrane 9 along which the applied sample migrates. See also column 4, lines 20-23, which clearly note that the conjugate pad 3 *overlaps* the membrane 9 so that the tracer and analyte are wicked on to the membrane together. This is the opposite of the structure in claim 6 wherein the tracer is beneath the surface of the test strip; Fredrickson instead shows the tracer suspended over the membrane in overlapping conjugate pad 3. A prima facie case of obviousness has not been established with respect to this claim. The cited reference does not show the claimed limitation, and in any event it would not be obvious to position the tracer in a place to retard its migration through the test strip of Boehringer, which has been specifically pretreated with methylated-BSA to avoid such differential migration.

Claims 8 and 9

Claim 8 states that the test strip is pretreated with at least one reagent that enhances the sensitivity of the assay device by delayed release immobilization of the tracer to the test strip that delays migration of the tracer along the test strip relative to migration of the analyte. Claim 9 lists several such agents. Prior Office actions had rejected this claim as obvious in view of Boehringer and Leuving, further in view of Terminiello et al. The Terminiello reference was said to disclose treating a membrane with polyvinyl pyrrolidone (PVP) to condition a membrane and reduce void space in the membrane. It was said to be obvious that the Boehringer membrane

should be treated with PVP to provide the advantages of reducing the void space in the matrix and assist or promote absorption of a fluid fraction of the biological sample.

However the combination of Boehringer with Leuvering and Terminiello would not produce the claimed structure of claim 8 in which the strip is pretreated with a reagent that enhances delayed release immobilization of the tracer in a strip in which the tracer migrates more slowly than the analyte. First it would frustrate the function of the methylated-BSA blocked test strips of Boehringer to modify them by providing delayed release immobilization of the tracer, because Boehringer teaches the importance of non-chromatographic flow through a bibulous matrix in which separation does not occur. Moreover, there is no disclosure in Terminiello of any delayed release immobilization in a test strip in which sequential migration occurs.

Terminiello appears to disclose only treating the entire membrane with PVP, which would reduce its pore size throughout the membrane. The claimed delayed release immobilization of the tracer to the test strip to delay migration of the tracer along the test strip relative to migration of the analyte would not be achieved by exposing the entire membrane to PVP as in Terminiello, because exposure of the entire membrane to this agent would reduce the size of all the pores. The proposed combination does not satisfy the structure of claim 8, and fails to establish a prima facie case of obviousness.

Claim 31

Claim 31 is a method of detecting and/or quantitating an analyte in a liquid sample by contacting the liquid sample with the test strip of claim 1, and allowing the liquid sample to mobilize tracer such that the distal flow of tracer migrates with the liquid sample, but reaches the primary capture zone after distal flow of analyte in the liquid sample. The Office actions

contended that Boehringer achieved the same result by using the same materials as in the claimed test strip. However the Boehringer test strip in every instance was blocked with methylated-BSA to eliminate bibulous flow and avoid chromatographic separation of the analyte and tracer. Hence a prima facie case of obviousness has not been established with respect to the method of claim 31 or the claims that depend from it.

Claim 45

Claim 45 is directed to a test kit that contains the test strip of claim 1, and instructions for using the test strip such that the flow of analyte in the liquid sample reaches the primary capture zone before the flow of tracer. Since the test strips of Boehringer have been blocked with methylated-BSA to eliminate non-bibulous flow in which such separation would occur, it would not be obvious to use the test strip of Boehringer in this manner. In the absence of a prima facie case of obviousness having been established, claim 45 is allowable.

The remaining claims are also allowable in view of the structure and steps set forth in those claims, and because they depend from claims that are allowable for the reasons set forth above.

Obviousness Type Double Patenting

A terminal disclaimer was filed in this case on December 2, 2005. The obviousness type double patenting rejection has therefore been obviated.

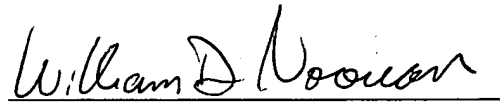
Conclusion

Since a prima facie case of obviousness has not been established, the claims are allowable. If any matters remain before a Notice of Allowance is issued, the examiner is invited to telephone the undersigned patent attorney.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By



William D. Noonan M.D.

Registration No. 30,878

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 228-9446